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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/507,387

05/09/2005

Dipankar Sen

CDM/2353.0010

1793

152 7590 08/05/2009
CHERNOFF, VILHAUER, MCCLUNG & STENZEL, LLP
601 SW Second Avenue
Suite 1600
PORTLAND, OR 97204-3157

EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

08/05/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/507,387	Applicant(s) SEN ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 5, 14, 24 and 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-13, 15-23, 25-27 and 29-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4-20-09</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Seq. Compliance Notice</u> . |

DETAILED ACTION

This Office action is in response to the communications filed 4-20-09 and 4-24-09.

Claims 1-39 are pending in the instant application.

Election/Restrictions

This application contains claims 5, 14, 24, 28, drawn to an invention nonelected without traverse in the reply filed on 6-20-08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Please delete the title of the application and replace it with the following, as indicated by Applicant:

-- DNA AND RNA CONFORMATIONAL SWITCHES AS SENSITIVE
ELECTRONIC SENSORS OF ANALYTES --.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-13, 15-23, 25-27, 29-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 10-16-08.

Applicant's arguments filed 4-20-09 have been fully considered but they are not persuasive. Applicant argues that insufficient reasons have been provided by the Examiner as to why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. Applicant argues that sufficiently detailed, relevant identifying characteristics have been provided, e.g. at paragraphs 10, 52-55, figures 1-2, and the Example commencing at paragraph 91. (It should be noted, however, that the instant specification does not have numbered paragraphs, but only has numbered pages and numbered lines). Applicant also argues that the specification at paragraph 6 describes in vitro selection methods for generating a wide variety of aptamer sequences capable of specifically binding a large number of different analytes,

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and that Figure 10 describes a process for in vitro selection methods for sensors specific for a particular target analyte. Applicant also argues that the Examiner has not addressed each of Applicant's claims separately, and that some of the claims are drawn to particular species, such as claim 29, which specifically relates to an adenosine analyte.

Contrary to Applicant's assertions, the disclosure does not provide adequate written description for the broad genus of compounds claimed. Applicant is correct that claim 29 is drawn to a sensor which receptor site binds an adenosine analyte, but adequate written description is lacking for the genus encompassing the adenosine biosensors for the reasons set forth below. In addition, the other claims are very broadly drawn, and encompass compositions and methods of detecting the presence of any analyte comprising providing at least one analyte sensor comprising first, second, third and fourth oligonucleotide stems which are multi-stranded DNA helices, connected together at either a three way or a four way junction, and wherein at least one of the first, second, and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally binds adenosine and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding the analyte, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is

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proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent, and which moiety is optionally rhodium III or anthraquinone, and which analyte sensor further comprises a detector which is a conductor electrically coupled to one of the oligonucleotide stems, and whereby the charge flow inducer triggers charge flow in one of the oligonucleotide stems, and a change is detected in charge transfer by electrically coupling a detector to the other one of the sensor stems, and changes are detected in the absence and presence of an analyte by measuring formation of oxidation products of the sensor, optionally including heating the sensor in the presence of piperidine and separating reaction products by gel electrophoresis.

Contrary to applicant's assertions, Figures 1-15 teach generalized schematics of sensor designs, and the text of the instant disclosure teaches a lack of correlation between the proposed sensors and their ability to provide predictable strand cleavage, predictable charge transport, or predictable and sensitive analyte detection, including in the presence of various concentrations of adenosine (See, for example, pages 26-29. On page 27, for instance, first full paragraph: "...i.e. strand cleavage was observed at the proximal (P) and distal (D) guanine doublets both in the absence (lane 4) or presence (data not shown) of 2mM adenosine..."). What's more, large differences in strand cleavage and charge transfer were also observed under different buffer conditions for the various purported sensors. See, e.g., page 28, first paragraph: "...A

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comparable enhancement, however, was not observed for the doublet (z) located in the third stem 22 (2-4 fold increase) as predicted by a structural model of this DNA construct...). See also, page 29, first full paragraph: "It remains unclear whether such differences reflect purely structural transformation of the aptamer in the different ionic strength solutions or whether they also reflect changes in the process of charge-transfer through DNA."

See also the third full paragraph on p. 29: "In addition, care must be taken in interpreting the results of the adenosine dependence data from Figure 14, since the curves may not directly reflect the binding affinities of the aptamer for its ligand... and it is unclear whether the binding of only one molecule of ligand allows charge transfer to occur to some extent or not."

While some details are provided for the concept of sensors in the instant disclosure, concise structural features of a representative number of species of the claimed genus are lacking. The specification and claims do not adequately describe the very broad genus comprising these analyte sensors. This broad genus encompasses a vast array of molecules and combination of subunits or component parts, and the disclosure fails to provide a representative number of species for the very broad genus which provide for the functions claimed, of predictably and accurately detecting any analyte, and which sensor or sensors reliably produce a signal upon converting to an excited, oxidized state upon a conformational change. The specification and claims do not adequately describe the concise structural features (e.g. polynucleotide sequences, structures of all component parts of the analyte sensor constructs) that distinguish

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structures within the broadly claimed genus from those without. The specification teaches schematics of mixed or composite sensors, and some examples of analyte sensors able to detect adenosine binding by adenosine specific aptamers, and utilizing guanine doublets to monitor charge transfer to the sensor and detector stems of adenosine sensors.

See also page 32, first full paragraph of the instant specification: "The ATP aptamer described in this Example possesses a dissociation constant in the mM range for the adenosine ligand. Such a binding affinity would be insufficient for a practical sensor intended to monitor, for instance, hormone levels in blood (for which, sensor-analyte affinities in the low nM to high pM range would be required." And, while the disclosure predicts that aptamers can be obtained using methods previously identified in the art, such as the SELEX method, a concise description of the actual construction of sensor molecules comprising analyte binding sites, and allowing predictable conformational changes in the presence of analytes in a solution that render predictable charge transfer and measurable signals, has not been provided. Written description takes into consideration what Applicant had in his possession at the time of filing, not what future experiments might produce.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species, requisite sequences, structural components, or higher order structures to describe the very broad genus comprising at least one analyte sensor comprising first, second, third and fourth oligonucleotide stems which are multi-stranded DNA helices, a receptor site which optionally binds any analyte

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and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding any analyte, which sensors are predictably alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of any analyte to the receptor site, switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state, and which provides for the function of detecting any analyte. The description provided in the instant disclosure does not adequately describe the elements, structures or sequences required for the broad genus claimed.

Thus, one of skill in the art would reasonably conclude that Applicant was not in possession of the broadly claimed genus. For these reasons, the instant rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-13, 15-23, 25-27, 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (US 2003/0087239) and Breaker (Current Opinion in Biotech., Vol. 13, pages 31-39, 2002) in view of the combined teachings of Meade et al (USPN 6,238,870), Berner et al (USPN 6,144,869), and Gasper et al (J. Am. Chem. Soc, Vol. 119, pages 12,762-12,771, 1997) for the reasons of record set forth in the Office action mailed 10-16-08.

Applicant's arguments filed 4-20-09 have been fully considered but they are not persuasive. Applicant argues that the combined teachings of record do not render the instant invention obvious. Applicant argues that none of the secondary references remedy the deficiencies of Stanton and Breaker. Applicant argues that Stanton does not teach a change in the electrical properties and charge transfer characteristics, but instead teaches changes in optical qualities of nucleic acid sensors, Breaker's disclosure is not related to changes in the transfer of electrical charge, Meade involves a covalently attached electron transfer moiety, Berner does not teach an electronic sensor system comprising oligonucleotide stems, and Gasper does not correlate the migration of oxidative damages in dsDNA to the sensing of analytes. Applicant

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additionally argues that there is no teaching, suggestion or motivation in either Stanton or Breaker for detecting binding of analytes electronically.

The claims are drawn compositions and methods of detecting the presence of an analyte comprising providing at least one analyte sensor comprising a first, second, third and fourth oligonucleotide stem, connected together at either a three way or a four way junction, and wherein at least one of the first, second, and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally is an aptamer which binds adenosine and which is operatively connected to the first oligonucleotide and second oligonucleotide stems, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent, and which moiety is optionally rhodium III or anthraquinone, and which analyte sensor further comprises a detector which is a conductor electrically coupled to the oligonucleotide stem, and whereby the charge flow inducer triggers charge flow in one of the oligonucleotide stems, and a change is detected in charge transfer by electrically coupling the detector to one of the sensor stems, and changes are detected in the

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absence and presence of adenosine by measuring formation of oxidation products of the sensor, and/or optionally including heating the sensor in the presence of piperidine and separating reaction products by gel electrophoresis.

Contrary to Applicant's assertions, one would have been motivated to combine the prior art teachings of Stanton and Breaker with those of Meade, Berner and Gasper in providing for an oligonucleotide based bioprobe that detects analytes through changes in charge transfer. Stanton, Breaker, Meade, and Berner teach the design of various biosensor molecules which rely on the detection of molecular changes (e.g. conformational or allosteric changes) as a result of analytes in a biological solution. These references differ in the modes of detection of the analytes, but the motivation to increase the sensitivities of biosensors is a resounding theme in the art.

The invention taught by Stanton makes use of a molecular switch which is activated upon binding of a target to a nucleic acid molecule, including an aptamer specific for a target molecule. The analyte detectors of Stanton include the binding of a target molecule by the sensor, resulting in changes in both the conformation and the physical aspect of the nucleic acid sensor molecule, wherein conformational changes in the nucleic acid sensor molecule upon target binding will modify the chemical environment of the signaling moiety, and whereby changes in the physical aspect of the nucleic acid sensor molecule will alter the kinetic properties of the signaling moiety, and these will lead to a detectable change in the detection properties of the nucleic acid sensor molecule.

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Likewise, Breaker teaches allosteric nucleic acids for analyte detection comprising a first, second, third and fourth oligonucleotide stem, connected together at either a three way or a four way junction, and wherein at least one of the first, second and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally is an aptamer which binds adenosine, and which is operatively connected to the first oligonucleotide and second oligonucleotide stems, which sensors are alterable between conformational states, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from one conformational state to a second conformational state which elicits a detectable signal, reflecting analyte binding.

Meade teaches the design, synthesis and use of nucleic acids as bioprobes, comprising charge flow inducers coupled to the nucleic acid molecules, which inducers include rhodium III, which functions as an oxidizing agent in an excited state, and which nucleic acid molecule further comprises a conductor, and which charge transfer is detected by coupling a detector to the nucleic acid molecule. Meade teaches the use of charge flow inducers, including rhodium, for enhancing the sensitivity of nucleic acids as bioprobes.

Berner teaches methods and devices for measuring analytes comprising biosensors and sensor elements that monitor electrical signals correlating with the

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concentration of a chemical compound, and which devices include a sensing electrode that converts an analyte or its derivative to an electrical signal. Berner teaches the use of rhodium as a conductor, which is optionally part of the biosensor system for converting an analyte or its derivative to a detectable electrical signal. Berner teaches the detection of electrochemical signals from the generation of a current which is proportional to the amount of analyte which is reacted.

Applicant is correct that Gasper does not teach biosensors, but Gasper is relied upon as a means for harnessing signals that may be conveyed throughout the nucleic acid-containing bioprobes - as a means of increasing the sensitivity of bioprobes after they bind their respective analytes. Gasper teaches the formation of quinine radicals in anthraquinone-derivatized DNA, e.g. after U.V. irradiation, and the migration of oxidative damage in throughout the nucleic acid molecule. Gasper teaches that radical cations formed from anthraquinone-derivatized DNA are able to migrate over the DNA molecule to distal portions of the DNA molecule, eventually causing strand breaks in parts of the DNA molecule that are far away from the site of the anthraquinone. Gasper also teaches that this migration of cation radicals can be interrupted by bulges in the DNA molecule.

Relying on the teachings of Gasper, one would have been motivated to utilize anthraquinone modified nucleic acids in biosensors because it was well known in the art that anthraquinone-derivatized DNA, after irradiation, allowed for migration of oxidative damage in nucleic acid molecules, which migration can be impeded upon perturbations

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caused by bulges or other conformational changes in the nucleic acid molecule (e.g. upon conformational changes of biosensors induced by analyte binding).

It would have been obvious to use allosteric nucleic acid biosensors previously taught by Stanton and Breaker, and optionally further comprising rhodium for increasing the detection of analytes in a solution because the use of allosteric biosensors was well known in the art to reduce the background for detecting analytes, as illustrated by Stanton and Breaker, and rhodium was well known in the art to increase the sensitivity of analyte detection because Meade teaches the use of charge flow inducers, including rhodium, for enhancing the sensitivity of nucleic acids as bioprobes and Berner teaches the use of rhodium as a conductor, which is optionally part of the biosensor system for converting an analyte or its derivative to a detectable electrical signal. One of skill in the art would have been motivated to utilize rhodium in such allosteric biosensors because rhodium was well known to conduct current and increase the sensitivity of nucleic acid probes when the current it conducts gets converted to an electrical signal. One of ordinary skill would have expected that the design and use of allosteric biosensors covalently modified with rhodium would provide for increased analyte sensitivity because the derivatization of nucleic acids with rhodium was well known in the art, as taught previously by Meade, and the conducive properties of rhodium were well known in the art, as taught previously by Berner, and the advantages of converting an analyte to an electrical signal using rhodium was known to provide for enhanced biosensitivity of sensors comprising rhodium. The solutions taught by Meade and Berner in increasing

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bioprobe sensitivity are logically combined with the prior art teachings of Stanton and Breaker in enhancing bioprobe sensitivity using previously existing technology.

One of ordinary skill in the art would have expected that applying the conjugation and chemical reactions taught previously by Meade, Berner, and Gasper to the allosteric biosensors previously taught by Stanton and Breaker would produce a more sensitive way of detecting analyte binding to biosensors, and that converting the analyte binding signal to an electric signal would provide for increased sensitivity of analyte binding, relying on the teachings of Berner.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-13, 15-23, 25-27, 29-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 12/102,669 for the reasons of record set forth in the Office action mailed 10-16-08. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions and methods of detecting the presence of any analyte comprising providing at least one analyte sensor comprising first and second oligonucleotide stems, and further comprising a receptor site which binds an analyte, and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding the analyte, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No arguments were made addressing this rejection.

Sequence Compliance Notice

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Please provide appropriate SEQ ID Nos. for the sequences recited in Figures 12 and 15 and where appropriate in the specification (e.g. description of the figures).**

See the accompanying Notice to Comply.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Jane Zara/

Primary Examiner, Art Unit 1635